(1390 REV. 5-93) US DEPT. OF COMMERCE PATENT & TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER
110048

U.S. APPLICATION NO.
(if known, sec 37 C.F.R.1.5)
09/869927

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/FR00/00144	January 21, 2000	January 21, 1999

TITLE OF INVENTION
ENDOGENEOUS NUCLEIC ACID FRAGMENT ASSOCIATED WITH AN AUTOIMMUNE DISEASE, LABELING METHOD AND REAGENT

APPLICANT(S) FOR DO/EO/US
Glaucia PARAHOS-BACCALA, Francois MALLET, Cecile VOISSET

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.

2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.

3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).

4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US)

6. ☒ A translation of the International Application into English (35 U.S.C. 371(c)(2)).

7. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.

8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).

9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).

10. ☒ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.

12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

13. ☒ A FIRST preliminary amendment.

    ☐ A SECOND or SUBSEQUENT preliminary amendment.

14. ☐ A substitute specification.

15. ☐ Entitlement to small entity status is hereby asserted.

16. ☐ Other items or information:

JC18 Rec'd PCT/PTO 0 9 JUL 2001

U.S. APPLICATION NO (if known, see 37 C.F.R. 1.5) 09/869927	INTERNATIONAL APPLICATION NO. PCT/FR00/00144	ATTORNEY'S DOCKET NUMBER 110048

17. ☒ The following fees are submitted:	CALCULATIONS	PTO USE ONLY
Basic National fee (37 CFR 1.492(a)(1)-(5)):		
Search Report has been prepared by the EPO or JPO $860.00		
International preliminary examination fee paid to USPTO (37 CFR1.482) $690.00		
No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) $710.00		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO $1,000.00		
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4) ..... $ 100.00		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$860.00	
Surcharge of $130.00 for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

Claims	Number Filed	Number Extra	Rate		
Total Claims	18 - 20 =	0	X $ 18.00	$	
Independent Claims	5 - 3 =	2	X $ 80.00	$160.00	
Multiple dependent claim(s)(if applicable)			+ $270.00	$	
TOTAL OF ABOVE CALCULATIONS =				$1020.00	
Reduction by 1/2 for filing by small entity, if applicable.			-	$	
SUBTOTAL =				$1020.00	
Processing fee of $130.00 for furnishing the English translation later than ☐ 20 ☐ 30 month from the earliest claimed priority date (37 CFR 1.492(f)).			+	$	
TOTAL NATIONAL FEE =				$1020.00	
				Amount to be refunded	$
				Charged	$

a. ☒ Check No. 120730 in the amount of $1020.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Director is hereby authorized to charge any additional fees which may be required, or credit any overpayment, to Deposit Account No. 15-0461. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:
OLIFF & BERRIDGE, PLC
P.O. Box 19928
Alexandria, Virginia 22320

NAME: William P. Berridge
REGISTRATION NUMBER: 30,024

NAME: Joel S. Armstrong
REGISTRATION NUMBER: 36,430

Date: July 9, 2001

(1390 Rev.10-00)

#4

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of

Glaucia PARANHOS-BACCALA et al. BOX: SEQUENCE

Application No.: 09/869,927

Filed: August 17, 2001 Docket No.: 110048

For: ENDOGENEOUS NUCLEIC ACID FRAGMENT ASSOCIATED WITH AN AUTOIMMUNE DISEASE, LABELING METHOD AND REAGENT

SUPPLEMENTAL PRELIMINARY AMENDMENT

Director of the U.S. Patent and Trademark Office
Washington, D.C. 20231

Sir:

In response to the Notification of Missing Requirements mailed August 21, 2001, please amend the above-identified patent application as follows:

IN THE SPECIFICATION:

At the end of the application, please replace the current Sequence Listing with the attached paper and computer-readable Sequence Listing.

Page 4, line 13 - page 5, line 18, delete current paragraph and insert therefor:

Location of the clones on the reconstructed genomic RNA sequence:

cl.6A2 (1321 bp) 1-1325;

cl.PH74 (535+2229= 2764 bp) 72-606 and 5353-7582;

cl.24.4 (491+1457= 1948 bp); 115-606 and 5353-6810;

cl.44.4 (2372 bp) 115-2496;

cl.PH7 (369+297= 666 bp) 237-606 and 7017-7313; cl.6A1 (2938 bp) 586-3559;

cl.Pi5T (2785+566= 3351 bp) 2747-5557 and 7017-7582;

cl.7A16 (1422 bp) 2908-4337;

cl.Pi22 (317+1689= 2006 bp) 3957-4273 and 4476-6168;

cl.C4C5 (1116 bp) 6467-7582

5'LTR 1..120

/note="R of 5'LTR (5' end uncertain)"

121..575

/note="U5 of 5'LTR"

misc. 579..596

/note="PBS, primer binding site, for tRNA-W"

misc. 606

/note="splice junction (splice donor site ATCCAAAGTG-GTGAGTAATA

(SEQ ID NO: 32) and splice acceptor site CTTTTTTCAG-ATGGGAAACG

(SEQ ID NO: 33), clone RG083M05, GenBank accession AC000064)"

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/note="splice acceptor site for ORF1 (env)"

misc. 5560

/note="splice donor site"

ORF 5581..7194

/note="ORF1 env 538 AA"

/product-="envelope"

misc. 7017

/note="splice acceptor site for ORF2 and ORF3"

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/note="ORF2 52 AA"

ORF 7112..7255

/note="ORF3 48 AA"

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/note="PPT, polypurine tract"

3'LTR 7256..7582

/note="U3-R of 3' LTR (U3-R junction undetermined)

misc. 7563..7569

polyadenylation signal

IN THE CLAIMS:

Please cancel claims 17 and 18 without prejudice to or disclaimer of the subject matter contained therein.

Please replace claim 12 as follows:

12. (Amended) Method for studying and/or monitoring T-cell proliferation in vitro, according to which the T cells from a patient are brought into contact with synthetic peptides belonging to SEQ ID NO. 31.

Please add new claims 19-31 as follows:

--19. Method according to claim 10, characterized in that the biological sample is a biological fluid chosen from serum, plasma, synovial fluid and urine.--

--20. Method for studying and/or monitoring T-cell proliferation in vitro, according to which the T cells from a patient are brought into contact with transcription/translation products as obtained according to the method of claim 19.--

--21. Reagent for detecting, in a biological sample, an autoimmune disease or monitoring pregnancy, comprising at least one transcription/translation product as obtained according to the method of claim 19.--

--22. Reagent for detecting, in a biological sample, an autoimmune disease or monitoring pregnancy, comprising at least one synthetic peptide belonging to SEQ ID NO: 31.--

--23. Reagent for detecting, in a biological sample, an autoimmune disease or monitoring pregnancy, comprising at least one protein according to claim 14.--

--24. A method for detecting susceptibility to an autoimmune disease or monitoring pregnancy of a patient, comprising bringing a biological sample of said patient into contact with at least one fragment according to claim 1.--

--25. The method of claim 24, wherein said autoimmune disease is multiple sclerosis.--

--26. A method for detecting susceptibility to an autoimmune disease or monitoring pregnancy of a patient, comprising bringing a biological sample of said patient into contact with at least one transcription/translation product as obtained according to the method of claim 19.--

--27. The method of claim 26, wherein said autoimmune disease is multiple sclerosis.--

--28. A method for detecting susceptibility to an autoimmune disease or monitoring pregnancy of a patient, comprising bringing a biological sample of said patient into contact with at least one synthetic peptide belonging to SEQ ID NO: 31.--

--29. The method of claim 28, wherein said autoimmune disease is multiple sclerosis.--

--30. A method for detecting susceptibility to an autoimmune disease or monitoring pregnancy of a patient, comprising bringing a biological sample of said patient into contact with at least one protein according to claim 14.--

--31. The method of claim 30, wherein said autoimmune disease is multiple sclerosis.--

REMARKS

Claims 1-16 and 19-31 are pending. Claims 17 and 18 are canceled; claim 12 is amended; and claims 19-31 are added herein.

Claims 19-23 are directed to subject matter deleted by the previous removal of multiple dependencies from the claims. Claims 24-31 are directed to subject matter corresponding to canceled use claims 17 and 18. Claim 12 is amended to remove an

dependency. However, the subject matter deleted from the claim has been

n of claim 20.

r copy and computer-readable copy of the Sequence Listing are

vith 37 C.F.R. §§1.821-1.825. The contents of the paper copy and

of the Sequence Listing are the same. No new matter is added. Support for the information provided in the Sequence Listing can be found in the original Sequence Listing and in the specification at page 4.

Prompt and favorable consideration on the merits is respectfully requested.

Respectfully submitted,

William P. Berridge
Registration No. 30,024

Melanie L. Mealy
Registration No. 40,085

WPB:MLM/jca

Attachments:
Appendix
Sequence Listing (paper and computer-readable copies)

Date: October 22, 2001

OLIFF & BERRIDGE, PLC
P.O. Box 19928
Alexandria, Virginia 22320
Telephone: (703) 836-6400

DEPOSIT ACCOUNT USE AUTHORIZATION
Please grant any extension necessary for entry;
Charge any fee due to our Deposit Account No. 15-0461

APPENDIX

Changes to Specification:

The Sequence Listing is replaced.

The following is a marked-up version of the amended paragraph:

Page 4, line 13 - page 5, line 18:

Location of the clones on the reconstructed genomic RNA sequence:

cl.6A2 (1321 bp) 1-1325;

cl.PH74 (535+2229= 2764 bp) 72-606 and 5353-7582;

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cl.PH7 (369+297= 666 bp) 237-606 and 7017-7313; cl.6A1 (2938 bp) 586-3559;

cl.Pi5T (2785+566= 3351 bp) 2747-5557 and 7017-7582;

cl.7A16 (1422 bp) 2908-4337;

cl.Pi22 (317+1689= 2006 bp) 3957-4273 and 4476-6168;

cl.C4C5 (1116 bp) 6467-7582

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/note="R of 5'LTR (5' end uncertain) ~~[sic]~~"

121..575

/note="U5 of 5'LTR"

misc. 579..596

/note="PBS, primer binding site, for tRNA-W"

misc. 606

/note="splice junction (splice donor site ATCCAAAGTG-GTGAGTAATA (SEQ ID NO: 32) and splice acceptor site CTTTTTTCAG-ATGGGAAACG (SEQ ID NO: 33), clone RG083M05, GenBank accession AC000064)"

misc. 5353

/note="splice acceptor site for ORF1 (env)"

misc. 5560

/note="splice donor site"

ORF 5581..7194

/note="ORF1 env 538 AA"

/product-="envelope"

misc. 7017

/note="splice acceptor site for ORF2 and ORF3"

ORF 7039..7194

/note="ORF2 52 AA"

ORF 7112..7255

/note="ORF3 48 AA"

misc. 7244..7254

/note="PPT, polypurine tract"

3'LTR 7256..7582

/note="U3-R of 3' LTR (U3-R junction undetermined)

misc. 7563..7569

polyadenylation signal

Changes to Claims:

Claims 17 and 18 are canceled.

Claims 19-31 are added.

The following is a marked-up version of the amended claim:

12. (Amended) Method for studying and/or monitoring T-cell proliferation in vitro, according to which the T cells from a patient are brought into contact with ~~either transcription/translation products, as obtained according to the method of claim 11, or~~ synthetic peptides belonging to SEQ ID NO. 31.

SEQUENCE LISTING

<110> PARANHOS-BACCALA, Glaucia

MALLET, Francois

VOISSET, Cecile

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<141> 2001-08-17

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Asp Arg Leu Arg Glu Ala Leu Arg Lys His Thr Ser Leu Ser Pro Asp
355 360 365

Ser Ile Glu Gly Gln Leu Ile Leu Lys Asp Lys Phe Ile Thr Gln Ser
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35 40 45

Phe Ile Phe Phe Cys Ser Thr Ala Trp Pro Gln Tyr Pro Leu Gln Gly
50 55 60

Arg Glu Thr Trp Leu Pro Glu Gly Ser Ile Asn Tyr Asn Ile Ile Leu
65 70 75 80

Gln Leu Asp Leu Phe Cys Arg Lys Glu Gly Lys Trp Ser Glu Val Pro
85 90 95

Tyr Val Gln Thr Phe Phe Ser Leu Arg Asp Asn Ser Gln Leu Cys Lys
100 105 110

Lys Cys Gly Leu Cys Pro Thr Gly Ser Pro Gln Ser Pro Pro Pro Tyr
115 120 125

Pro Ser Val Pro Ser Pro Thr Pro Ser Ser Thr Asn Lys Asp Pro Pro
130 135 140

Leu Thr Gln Thr Val Gln Lys Glu Ile Asp Lys Gly Val Asn Asn Glu
145 150 155 160

Pro Lys Ser Ala Asn Ile Pro Arg Leu Cys Pro Leu Gln Ala Val Arg
165 170 175

Gly Gly Glu Phe Gly Pro Ala Arg Val Pro Val Pro Phe Ser Leu Ser
180 185 190

Asp Leu Lys Gln Ile Lys Ile Asp Leu Gly Lys Phe Ser Asp Asn Pro
195 200 205

Asp Gly Tyr Ile Asp Val Leu Gln Gly Leu Gly Gln Ser Phe Asp Leu
210 215 220

Thr Trp Arg Asp Ile Met Leu Leu Leu Asn Gln Thr Leu Thr Pro Asn
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Glu Arg Ser Ala Ala Val Thr Ala Ala Arg Glu Phe Gly Asp Leu Trp
245 250 255

Tyr Leu Ser Gln Ala Asn Asn Arg Met Thr Thr Glu Glu Arg Thr Thr
260 265 270

Pro Thr Gly Gln Gln Ala Val Pro Ser Val Asp Pro His Trp Asp Thr
275 280 285

Glu Ser Glu His Gly Asp Trp Cys His Lys His Leu Leu Thr Cys Val
290 295 300

Leu Glu Gly Leu Arg Lys Thr Arg Lys Lys Pro Met Asn Tyr Ser Met
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Met Ser Thr Ile Thr Gln Gly Lys Glu Glu Asn Leu Thr Ala Phe Leu
325 330 335

Asp Arg Leu Arg Glu Ala Leu Arg Lys His Thr Ser Leu Ser Pro Asp
340 345 350

Ser Ile Glu Gly Gln Leu Ile Leu Lys Asp Lys Phe Ile Thr Gln Ser
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<212> DNA

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PCT09

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PATENT APPLICATION: US/09/869,927

DATE: 12/19/2001 8.5
TIME: 16:12:55

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13       VOISSET, Cecile
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    50                  55                  60
Phe Ile Phe Phe Cys Ser Thr Ala Trp Pro Gln Tyr Pro Leu Gln Gly
65                  70                  75                  80
Arg Glu Thr Trp Leu Pro Glu Gly Ser Ile Asn Tyr Asn Ile Ile Leu
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Gln Leu Asp Leu Phe Cys Arg Lys Glu Gly Lys Trp Ser Glu Val Pro
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Tyr Val Gln Thr Phe Phe Ser Leu Arg Asp Asn Ser Gln Leu Cys Lys
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Lys Cys Gly Leu Cys Pro Thr Gly Ser Pro Gln Ser Pro Pro Pro Tyr
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Pro Lys Ser Ala Asn Ile Pro Arg Leu Cys Pro Leu Gln Ala Val Arg
            180                 185                 190
Gly Gly Glu Phe Gly Pro Ala Arg Val Pro Val Pro Phe Ser Leu Ser
        195                 200                 205
Asp Leu Lys Gln Ile Lys Ile Asp Leu Gly Lys Phe Ser Asp Asn Pro
    210                 215                 220
Asp Gly Tyr Ile Asp Val Leu Gln Gly Leu Gly Gln Ser Phe Asp Leu
225                 230                 235                 240
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                245                 250                 255
Glu Arg Ser Ala Ala Val Thr Ala Ala Arg Glu Phe Gly Asp Leu Trp
            260                 265                 270
Tyr Leu Ser Gln Val Asn Asn Arg Met Thr Thr Glu Glu Arg Thr Thr
        275                 280                 285
Pro Thr Gly Gln Gln Ala Val Pro Ser Val Asp Pro His Trp Asp Thr
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Leu Glu Gly Leu Arg Lys Thr Arg Lys Lys Pro Met Asn Tyr Ser Met
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RAW SEQUENCE LISTING DATE: 12/19/2001
PATENT APPLICATION: US/09/869,927 TIME: 16:12:55

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 906     130                 135                 140
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 914 145                 150                 155                 160
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 922                 165                 170                 175
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 930             180                 185                 190
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 938         195                 200                 205
 944 Asp Gly Tyr Ile Asp Val Leu Gln Gly Leu Gly Gln Ser Phe Asp Leu
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 952 Thr Trp Arg Asp Ile Met Leu Leu Leu Asn Gln Thr Leu Thr Pro Asn
 954 225                 230                 235                 240
 960 Glu Arg Ser Ala Ala Val Thr Ala Ala Arg Glu Phe Gly Asp Leu Trp
 962                 245                 250                 255
 968 Tyr Leu Ser Gln Ala Asn Asn Arg Met Thr Thr Glu Glu Arg Thr Thr
 970             260                 265                 270
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Use of n and / or Xaa has been detected in the Sequence Listing. Review the Sequence Listing to ensure a corresponding explanation is present in the <220> to <223> fields of each sequence using n or Xaa.

VERIFICATION SUMMARY DATE: 12/19/2001
PATENT APPLICATION: **US/09/869,927** TIME: 16:12:56

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L:3499 M:341 W: (46) "n" or "Xaa" used, for SEQ ID#:30

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of

Glaucia PARANHOS-BACCALA, Francois MALLET,
Cecile VOISSET

Application No.: US National Stage of PCT/FR00/00144

Filed: July 9, 2001 Docket No.: 110048

For: ENDOGENEOUS NUCLEIC ACID FRAGMENT ASSOCIATED WITH AN AUTOIMMUNE DISEASE, LABELING METHOD AND REAGENT

PRELIMINARY AMENDMENT

Director of the U.S. Patent and Trademark Office
Washington, D. C. 20231

Sir:

Prior to initial examination, please amend the above-identified application as follows:

IN THE CLAIMS:

Please replace claims 7, 11, 16 and 17 as follows:

7. (Amended) Transcription product which can be obtained by transcription of at least said portion of the *gag* gene of a fragment according to claim 1.

11. (Amended) Method according to claim 8, characterized in that the biological sample is a biological fluid chosen from serum, plasma, synovial fluid and urine.

16. (Amended) Reagent for detecting, in a biological sample, an autoimmune disease or monitoring pregnancy, comprising at least one fragment according to claim 1.

17. (Amended) Use of a fragment according to claim 1, for detecting, in a biological sample, susceptibility to an autoimmune disease, or monitoring pregnancy.

REMARKS

Claims 1-18 are pending. Claims 7, 11, 16 and 17 are amended to eliminate multiple dependencies. Prompt and favorable consideration on the merits is respectfully requested.

The attached Appendix includes marked-up copies of each rewritten claim (37 C.F.R. §1.121(c)(1)(ii)).

Respectfully submitted,

William P. Berridge
Registration No. 30,024

Joel S. Armstrong
Registration No. 36,430

WPB:JSA/zmc

Attached: APPENDIX

Date: July 9, 2001

OLIFF & BERRIDGE, PLC
P.O. Box 19928
Alexandria, Virginia 22320
Telephone: (703) 836-6400

DEPOSIT ACCOUNT USE AUTHORIZATION
Please grant any extension necessary for entry;
Charge any fee due to our Deposit Account No. 15-0461

APPENDIX

Changes to Claims:

The following are marked-up versions of the amended claims:

7. (Amended) Transcription product which can be obtained by transcription of at least said portion of the *gag* gene of a fragment according to claim 1~~any one of claims 1 to 6~~.

11. (Amended) Method according to claim 8~~any one of claims 8 to 10~~, characterized in that the biological sample is a biological fluid chosen from serum, plasma, synovial fluid and urine.

16. (Amended) Reagent for detecting, in a biological sample, an autoimmune disease or monitoring pregnancy, comprising at least one fragment according to claim 1.~~any one of claims 1 to 6, one transcription/translation product, as obtained according to the method of claim 11, one sythentic peptide belonging to SEQ ID NO. 31 or one protein according to claim 15 or 16.~~

17. (Amended) Use of a fragment according to claim 1~~any one of claims 1 to 6, of a transcription/translation product, as obtained according to the method of claim 11, one sythentic peptide belonging to SEQ ID NO. 31 or one protein according to claim 15 or 16~~, for detecting, in a biological sample, susceptibility to an autoimmune disease, or monitoring pregnancy.

ENDOGENEOUS NUCLEIC ACID FRAGMENT ASSOCIATED WITH AN AUTOIMMUNE DISEASE, LABELING METHOD AND REAGENT

The present invention relates to an endogenous nucleic acid fragment of the retroviral type, integrated into the DNA of the human genome.

Retroviruses are RNA viruses which replicate through a process termed reverse transcription, mediated by an RNA-dependent DNA polymerase named reverse transcriptase (RT), which is encoded by the *pol* gene. The retroviral RNA also comprises at least two additional genes, which are the *gag* and *env* genes. The *gag* gene encodes the proteins of the backbone, i.e. the matrix, the capsid and the nucleocapsid. The *env* gene encodes the envelope proteins. The transcription is regulated by promoter regions located in the LTRs (Long Terminal Repeat) which border the 5'- and 3'-terminal ends of the retroviral genome.

In the course of evolution, humans or their ancestors have integrated material of retroviral origin into their genome subsequent to an infection. Specifically, when a cell is infected, the reverse transcriptase makes a DNA copy of the retroviral RNA, and this DNA copy may then possibly integrate into the human genome. Retroviruses can infect germinal cells and thus be transmitted to future generations by vertical Mendelien transmission. They are then referred to as endogenous retroviruses which are present in the form of proviral DNA integrated into the genome of all human cells. Most endogenous retroviruses are silent or defective. However, some of them have been able to conserve all or part of their initial properties and may be activated under specific conditions. The expression of endogenous retroviruses can range from the transcription of viral genes to the production of viral particles.

These endogenous retroviruses may be associated directly or indirectly with the development of certain pathological conditions.

Endogenous retroviral structures may be in a complete LTR-gag-pol-env-LTR form or in truncated forms.

Thus, in a previous patent application (PCT/FR98/01442), the applicant screened a cDNA library using a Ppol-MSRV probe (SEQ ID NO. 18) and detected overlapping clones which allowed it to reconstruct a putative genomic RNA of 7582 nucleotides. This genomic RNA has an R-U5-gag-pol-env-U3-R structure. A "blastn" interrogation over several databases using the reconstructed genome made it possible to show that there is a considerable amount of related genomic (DNA) sequences in the human genome, which are found on several chromosomes. Thus, the applicant demonstrated the existence of partial structures of the retroviral type in the human genome and envisaged their potential role in the development of autoimmune diseases, in unsuccessful pregnancy or pathological conditions of pregnancy.

Autoimmune diseases which may be mentioned by way of example are multiple sclerosis, rhumatoid arthritis, lupus erythematosus disseminatus, insulin-dependent diabetes and/or pathologies which are associated with them.

The isolation and sequencing of overlapping cDNA fragments and the identification of genomic (DNA) clones corresponding to the isolated DNA clones, described in the applicant's abovementioned PCT patent application, are incorporated herein by way of reference.

Isolation and sequencing of overlapping cDNA fragments:

The information regarding the organization of the novel family of endogenous retroviruses named, by the applicant, HERV-W was obtained by testing a placenta cDNA library (Clontech cat#HL5014a) with the Ppol-MSRV (SEQ ID NO. 18) and Penv-C15 (SEQ ID NO. 19) probes and then carrying out a "gene walking" technique using the novel sequences obtained. The experiments were carried out with reference to the recommendations of the supplier of the library. PCR amplifications on DNA were also used in order to understand this organization.

The following clones were selected and sequenced:

- Clone cl.6A2 (SEQ ID NO. 20): 5' untranslated region of HERV-W and a portion of gag.
- Clone cl.6A1 (SEQ ID NO. 21): gag and a portion of pol.
- Clone cl.7A16 (SEQ ID NO. 22): 3' region of pol.
- Clone cl.Pi22 (SEQ ID NO. 23): 3' region of pol and start of env.
- Clone cl.24.4 (SEQ ID NO. 24): spliced RNA comprising a portion of the 5' untranslated region of HERV-W, the end of pol and the 5' region of env.
- Clone cl.C4C5 (SEQ ID NO. 25): end of env and 3' untranslated region of HERV-W.
- Clone cl.PH74 (SEQ ID NO. 26): subgenomic RNA: 5' untranslated region of HERV-W, end of pol, env, and 3' untranslated region of HERV-W.
- Clone cl.PH7 (SEQ ID NO. 27): multispliced RNA: 5' untranslated region of HERV-W, end of env and 3' untranslated region of HERV-W.
- Clone cl.Pi5T (SEQ ID NO. 28): partial pol gene and U3-R region.
- Clone cl.44.4 (SEQ ID NO. 29): R-U5 region, gag gene and partial pol gene.

A total sequence model for HERV-W was produced with the aid of these clones, by carrying out sequence alignments. The spliced RNAs were revealed and also the potential splice donor and acceptor sites. The LTR, gag, pol and env entities were defined by studying similarity with existing retroviruses.

The putative genetic organization of HERV-W in the RNA form is as follows (SEQ ID NO. 30):

gene 1..7582.

Location of the clones on the reconstructed genomic RNA sequence:
cl.6A2 (1321 bp) 1-1325;
cl.PH74 (535+2229= 2764 bp) 72-606 and 5353-7582;
cl.24.4 (491+1457= 1948 bp); 115-606 and 5353-6810;
cl.44.4 (2372 bp) 115-2496;
cl.PH7 (369+297= 666 bp) 237-606 and 7017-7313; cl.6A1 (2938 bp) 586-3559;
cl.Pi5T (2785+566= 3351 bp) 2747-5557 and 7017-7582;
cl.7A16 (1422 bp) 2908-4337;
cl.Pi22 (317+1689= 2006 bp) 3957-4273 and 4476-6168;
cl.C4C5 (1116 bp) 6467-7582
5'LTR 1..120
/note="R of 5'LTR (5' end uncertain [sic]"
121..575
/note="U5 of 5'LTR"
misc. 579..596
/note="PBS, primer binding site, for tRNA-W"
misc. 606
/note="splice junction (splice donor site ATCCAAAGTG-GTGAGTAATA and splice acceptor site CTTTTTTCAG-ATGGGAAACG, clone RG083M05, GenBank accession AC000064)"
misc. 5353
/note="splice acceptor site for ORF1 (env)"
misc. 5560

/note="splice donor site"
ORF 5581..7194
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/product-="envelope"
misc. 7017
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ORF 7039..7194
/note="ORF2 52 AA"
ORF 7112..7255
/note="ORF3 48 AA"
misc. 7244..7254
/note="PPT, polypurine tract"
3'LTR 7256..7582
/note="U3-R of 3' LTR (U3-R junction undetermined)
misc. 7563..7569
polyadenylation signal

Identification of genomic (DNA) clones corresponding to the isolated DNA clones:

A "blastn" interrogation over several databases, using the reconstructed genome, showed that there is a considerable amount of related sequences in the human genome. Approximately 400 sequences were identified in GenBank and more than 200 sequences in the EST bank, most of them in the antisense orientation. The 4 most significant sequences in terms of size and similarity are the sequences of the following genomic (DNA) clones:

Human clone RG083M05 (gb AC000064), the chromosomal location of which is 7q21-7q22,

Human clone BAC378 (gb U85196, gb AE000660) corresponding to the alpha/delta locus of the T-cell receptor, located at 14q11-12,

Human cosmid Q11M15 (gb AF045450) corresponding to region 21q22.3 of chromosome 21,

Cosmid U134E6 (embl Z83850) on chromosome Xq22.

The location of the aligned regions for each of the clones is indicated and the chromosome to which they belong is indicated between square brackets (Figure 6 [sic]). The percentage similarity (without the large deletions) between the 4 sequences and the reconstructed genomic RNA is indicated, and also the presence of repeat sequences at each end of the genome and the size of the longest open reading frames (ORFs). Repeat sequences were found at the ends of 3 of these clones. The reconstructed sequence is entirely contained within clone RG083M05 (9.6 Kb) and exhibits 96% similarity. However, clone RG083M05 has a 2 Kb insertion located immediately downstream of the 5' untranslated region (5' UTR). This insertion is also found in two other genomic clones which have a 2.3 Kb deletion immediately upstream of the 3' untranslated region (3' UTR). No clone contained the three functional gag, pol and env open reading frames (ORFs). Clone RG083M05 shows a 538 amino acid (AA) ORF corresponding to a whole envelope. Cosmid Q11M15 contains two major contiguous ORFs of 413 AA (frame 0) and 305 AA (frame +1) corresponding to a truncated pol polyprotein.

An endogenous nucleic acid fragment has now been found and isolated, which is integrated into the DNA of the human genome and which comprises or consists of at least one portion of the *gag* gene of an endogenous retrovirus associated with an autoimmune disease, or with unsuccessful pregnancy or pathological conditions of pregnancy, this portion at least encoding, directly or indirectly, an expression product. Of course, the invention also comprises the sequence complementary to said fragment.

Advantageously, the fragment defined above also satisfies at least any one of the following characteristics:

It comprises, or consists of, said whole *gag* gene;

Said portion of the fragment at least encodes the matrix and the capsid;

It comprises, or consists of, SEQ ID NO. 1, SEQ ID NO. 2, SEQ ID NO. 3 or the sequence complementary to any one of said sequences;

It is located on at least one of human chromosomes 1, 3, 6, 7 and 16, it is preferably located on at least chromosome 3;

The product of expression of said portion is messenger RNA;

The product of expression of said portion is immunologically recognized by antibodies present in a biological sample from a patient suffering from an autoimmune disease, such as multiple sclerosis; preferably, the biological fluid is chosen from serum, plasma, synovial fluid and urine.

Another subject of the invention is an endogenous transcription product which is in isolated form and which can be obtained by transcription of at least said portion of the *gag* gene of a fragment of the invention.

The invention also relates to a method for detecting endogenous nucleotide sequences belonging to a fragment of the invention, comprising the following steps:

a prior step of extraction of the cellular DNA from a tissue or biological fluid is carried out, and then at

least one cycle of amplification of the cellular DNA is carried out, for instance by PCR, using primers in particular chosen from SEQ ID NO. 4 to SEQ ID NO. 9 and SEQ ID NO. 12 to SEQ ID NO. 17,

the cellular DNA present in the sample is brought into contact with a given probe which is capable of hybridizing with a fragment as defined above and of forming a hybridization complex, said probe comprising at least 15 contiguous nucleotides, preferably 17 and advantageously 19 contiguous nucleotides, of SEQ ID NO. 3, or consisting of SEQ ID NO. 3, under suitable conditions for the hybridization, in particular under conditions of high stringency, and

the hybridization complexes formed are detected by any suitable means.

Advantageously, the probe is labeled with a tracer, such as for example a radioactive tracer or an enzyme.

The invention also relates to a method for detecting endogenous nucleotide sequences belonging to a fragment of the invention, comprising the following steps:

a prior step of extraction of the cellular DNA from a tissue or biological fluid is carried out, and then at least one cycle of amplification of the cellular DNA is carried out, for instance by PCR, using primers in particular chosen from SEQ ID NO. 4 to SEQ ID NO. 9 and SEQ ID NO. 12 to SEQ ID NO. 17,

a step of in vitro transcription/translation of the amplified product is carried out, and

the product derived from the transcription/translation step is reacted with a serum or plasma from a patient with an autoimmune disease.

The invention also relates to a method for studying and/or monitoring T-cell proliferation in vitro, according to which the T cells from a patient are brought into contact with either transcription/translation products (SEQ ID NO. 31), as obtained according to the method above, or synthetic peptides derived from or belonging to SEQ ID NO. 31.

Another subject of the invention is a method for the in situ molecular labeling of chromosomes isolated from patients, in which a probe labeled with any suitable tracer, and comprising all or part of SEQ ID NO. 3, is used.

The invention also relates to:

a recombinant protein obtained using an expression cassette in a bacterial host, characterized in that its protein sequence consists of SEQ ID NO. 31; the bacterial host is in particular *E. coli*;

a reagent for detecting an autoimmune disease or monitoring pregnancy, comprising at least one fragment or one protein of the invention;

the use of a fragment or of a protein of the invention for detecting, in a biological sample, susceptibility to an autoimmune disease, or monitoring pregnancy; in particular, the autoimmune disease is multiple sclerosis.

Before setting out the present invention in greater detail, the definition of certain terms employed in the description and claims is given.

The expression "expression product" means any product derived from the retroviral DNA integrated into the

human genome, including the transcription products (messenger RNA) and the products derived from the translation of the messenger RNA obtained. In the latter case, and by way of example, the product may be a peptide or a protein which is functional or functionalizable, i.e. which can become functional.

The expression "portion encoding, directly or indirectly, an expression product" is intended to mean a portion which, by itself, comprises at least all or part of an open reading frame from which it is possible to deduce an amino acid sequence, and the coding capacity of which can be induced by elements such as, for example, those which may have promoter activity. This definition includes the variability which may be found in the coding nucleic acid sequence, provided that the above conditions are respected.

Example 1: Location of the *gag* gene of the HERV-W family on human chromosomes using the Southern blot technique

In order to locate the *gag* gene of the HERV-W family, a probe corresponding to this gene from MSRV was hybridized on a nylon membrane (Hybond® N+, Amersham) containing 5 µg of DNA from 24 somatic cell hybrids [human x rodents] (isolated human genomic DNA: 22 autosomal chromosomes and 2 sex chromosomes) and 3 control DNAs (human, mouse and hamster), digested with the EcoRI restriction enzyme.

The following probe is used: Pgag-C12 identified by SEQ ID NO. 3 corresponding to the coding region (of 1056 bp) of the clone MSRV gag C12.

1.1- Production of clone 2, C12, containing, in the 3' region, a portion homologous to the *pol* gene, corresponding to the protease gene, and a portion

homologous to the *gag* gene, corresponding to the nucleocapsid, and a 5' coding region, corresponding to the *gag* gene, more specifically the matrix and capsid of MSRV-1.

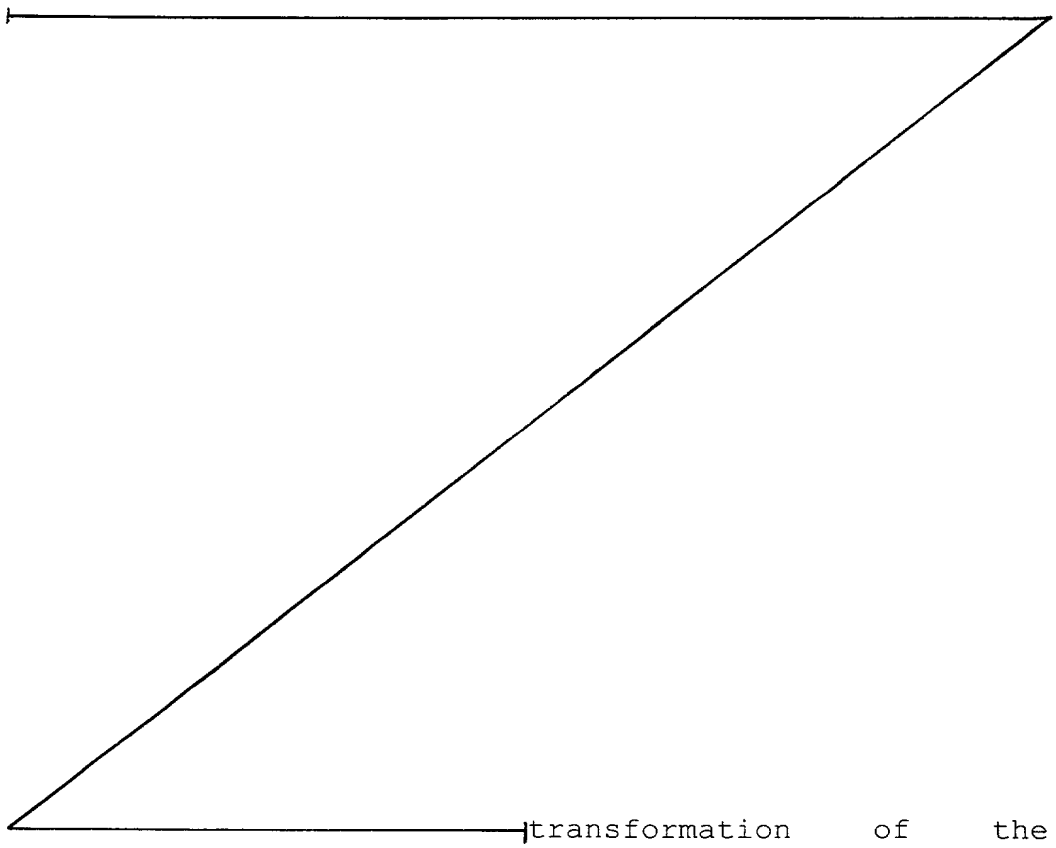
A PCR amplification was carried out on total RNA extracted from 100 µl of plasma from a patient suffering from MS. A water control, treated under the same conditions, was used as a negative control. The cDNA synthesis was carried out with 300 pmol of a random primer (Gibco-BRL, France) and the "Expand RT" reverse transcriptase (Boehringer Mannheim, France), according to the conditions recommended by the company. A PCR (polymerase chain reaction) amplification was carried out with the *Taq* polymerase enzyme (Perkin Elmer, France) using 10 µl of cDNA under the following conditions: 94°C 2 min, 55°C 1 min and 72°C 2 min, then 94°C 1 min, 55°C 1 min and 72°C 2 min for 30 cycles and 72°C for 7 min, with a final reaction volume of 50 µl.

The primers used for the PCR amplification are as follows:

- 5' primer, identified by SEQ ID NO. 4
5' CGG ACA TCC AAA GTG ATG GGA AAC G 3';
- 3' primer, identified by SEQ ID NO. 5
5' GGA CAG GAA AGT AAG ACT GAG AAG GC 3'

A second "nested" PCR amplification was carried out with 5' and 3' primers located inside the region already amplified. This second PCR was carried out under the same experiment conditions as those used in the first PCR, using 10 µl of the amplification product derived from the first PCR.

The primers used for the nested PCR amplification are as follows:



transformation of the ligation in *E. coli* bacteria, the ligation mixture was plated out. At the end of the procedure, the white colonies of recombinant bacteria were picked in order to be cultured and to allow the extraction of the incorporated plasmids according to the "DNA minipreparation" procedure (J. Sambrook, E.F. Fritsch and T. Maniatis, Molecular Cloning, a laboratory manual, Cold Spring Harbour Laboratory Press, 1989). The plasmid preparation from each recombinant colony was cleaved with the Eco RI restriction enzyme and analyzed on agarose gel. The plasmids possessing an insert which was detected under UV light after staining the gel with ethidium bromide were selected in order to sequence the insert after hybridization with a primer complementary to the T7 promoter present on the cloning plasmid from the TA Cloning Kit®. The reaction prior to the sequencing was then carried out according to the method recommended for using the "Prism® Ready Reaction

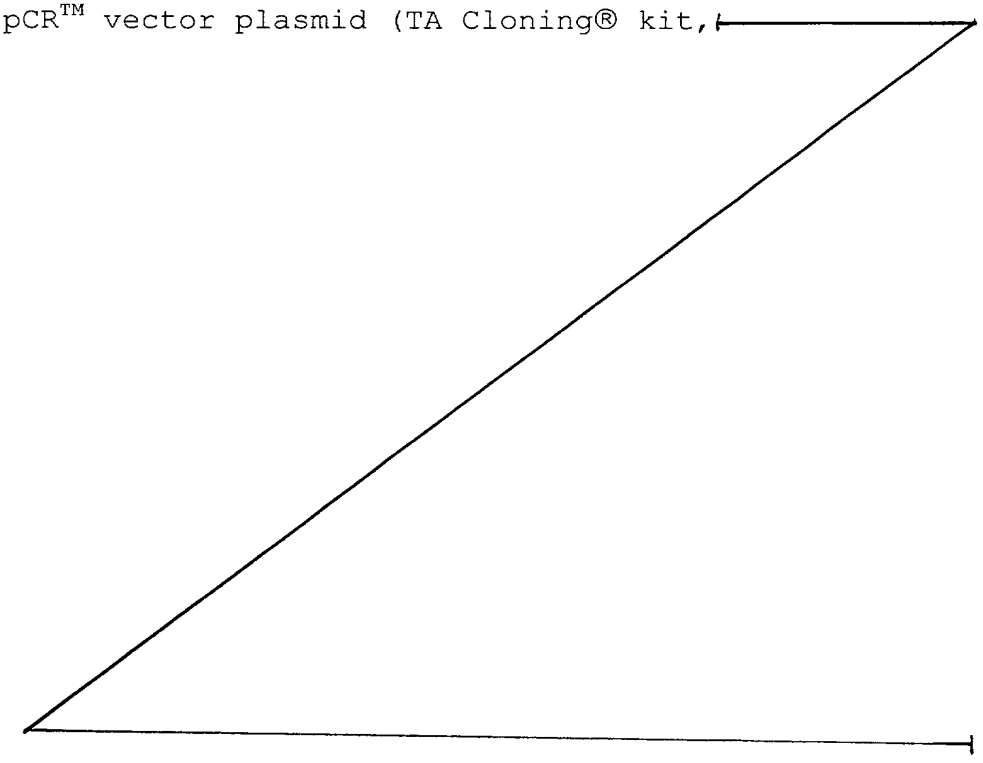
Amplitaq® FS, DyeDeoxy™ Terminator" sequencing kit (Applied Biosystems, ref. 402119) and the automatic sequencing was carried out on the Applied Biosystems 373 A and 377 machines, according to the manufacturer's instructions.

The clone obtained, named C12, makes it possible to define a 1511 bp region which has an open reading frame in the N-terminal region of 1089 bp (fragment 434-1521 of SEQ ID NO. 2) encoding 363 amino acids (SEQ ID NO. 31) corresponding to the matrix and capsid regions of the *gag* gene.

The nucleotide sequence of C12 is identified by SEQ ID NO. 1. It is represented in Figure 2 with the potential amino acid reading frames.

1.2- Production of the MSRV gag c12 probe

The probe was obtained after PCR amplification, using the pCR™ vector plasmid (TA Cloning® kit,



out and labeled with [α-P^{32}] using random primers (Gibco-BRL, France) in accordance with instructions of the "Ready-to-go DNA labeling" kit (Pharmacia Biotech). The unincorporated nucleotides were removed with a G-50 Quick Spin column (Boehringer, Mannheim).

1.3- Southern blot

The hybridization conditions are as follows:

After prehybridization for 4 hours (in 5X SSC, 1X Denhardt's, 0.1% SDS, 50% formamide, 20 mM Tris-HCl, pH = 7.5, and 0.1 mg/ml of herring sperm DNA), the nylon membrane containing the human chromosomes was hybridized (in 5X SSC, 1X Denhardt's, 0.1% SDS, 50% formamide, 20 mM Tris-HCl, pH = 7.5, 0.1 mg/ml of herring sperm DNA and 5% dextran sulfate) for 18 hours at 42°C with the ^{32}P-labeled 1056 bp gag cl2 DNA probe (SEQ ID NO. 3). After hybridization, the membrane (The BIOS Monochromosomal Somatic Cell Hybrid blot, from Quantum Bioprobe) hybridized with the gag probe was washed twice in 2X SSC/0.2% SDS solution for 15 min at room temperature, and twice (in 0.2X SSC/0.2% SDS) for 15 min at 45°C. After washing, the membrane was exposed to the X-ray film at -80°C in the presence of an amplifying screen.

The results are given in Table 1 hereinafter.

In this table:

m, which signifies mouse, and h, which signifies hamster, correspond to the recipient cells for the human chromosomal DNA.

The number indicated under each chromosome corresponds to the number of bands encountered.

The total number of copies of the gag gene is 66.

Table 1

Chromo No. Rodent parent	1 m	2 h	3 h	4 h	5 h	6 h	7 h	8 h	9 h	10 h	11 h	12 h	13 h	14 h	15 h	16 m	17 m	18 h	19 h	20 m	21 m	22 h	X h	Y h	Mouse	Hamster
Gag probe	5	0	6	6	5	3	2	3	2	4	3	6	3	1	3	0	3	2	1	0	4	0	4	0	0	0

Example 2: PCR amplification of the *gag* gene of the HERV-W family on each of the isolated human chromosomes; verification of the specificity of the amplifications by Southern blot; "in vitro" transcription/translation (PTT) test using the PCR products, in order to verify the coding capacity and discover which of the human chromosomes have open reading frames for the gag gene of the HERV-W family.

2.1- PCR amplification

In order to amplify the HERV-W *gag* gene, a PCR was carried out on each isolated human chromosome [*NIGMS human/rodent somatic cell hybrid panel #2*. The human monochromosomal NIGMS somatic hybrid mapping panel #2, described by H.L. Drwinga et al. and B.L. Dubois et al., obtained from the Coriell Institute (Camden, NJ)] with the *Taq* polymerase enzyme (Perkin Elmer, France) using: 40 pmol of each primer, 25 mM of each dNTP (Pharmacia), 2.5 mM of $MgCl_2$, 2.5 U of *Taq* polymerase in the standard PCR buffer (Perkin Elmer) and 300 ng of isolated chromosome DNA, in a final volume of 100 µl. The PCR conditions for amplifying the *gag* region are as follows: 3 min at 94°C; then 1 min at 94°C, 1 min at 55°C and 3 min at 72°C for 30 cycles, and 7 min at 72°C.

The primers used for the PCR amplification of the *gag* gene, from an ATG introduced into the HERV-W gag sequence on each isolated human chromosome are as follows:

- 5' primer, identified by SEQ ID NO. 14
5'-TTT GGT AAT ACG ACT CAC TAT AGG GCA GCC ACC ATG GGA AAC GTT CCC CCC GAG-3'.

The primer contains the T7 RNA polymerase promoter sequence, a "spacer", the Kozak sequence (translation

initiation site in eukaryotes) and the 5' gag sequence starting from the HERV-W ATG.

- 3' primer, identified by SEQ ID NO. 15

5'-TTTTTTTTTTTTTTTTTTTCAGGCTGCGCCAGTGTCCAGGAGAC-3'.

The primer contains a poly-A tail (in order to stabilize the transcription of the RNA, represented by 18 T bases), a stop codon (represented by TCA) and the sequence of the MSRV-1 protease gene (G+E+A).

For the amplification of the HERV-W *gag* gene using oligonucleotides defined in the LTR and protease regions of HERV-W, with the *Taq* polymerase enzyme (Perkin Elmer, France), the PCR conditions were as follows: 3 min at 94°C; then 1 min at 94°C, 1 min at 60°C and 2 min at 72°C, 35 cycles; followed by 7 min at 72°C, with 50 ng of each monochromosomal DNA.

The primers used for the PCR amplification of the *gag* gene using the oligonucleotide defined in the HERV-W LTR sequence, on each isolated human chromosome, are as follows:

- 5' primer, identified by SEQ ID NO. 16

5'-TGTCCGCTGTGCTCCTGATC-3'

- 3' primer, identified by SEQ ID NO. 17

5'-TTTTTTTTTTTTTTTTTTTCAGGCTGCGCCAGTGTCCAGGAGAC-3'.

The primer contains a poly-A tail (in order to stabilize transcription of the RNA, represented by 18 T bases), a stop codon (represented by TCA) and the sequence of the MSRV-1 G+E+A protease gene.

The PCR amplifications were carried out in an MJ Research PTC200 Peltier Thermal cycler machine. The PCR products (10 µl of each PCR product) were analyzed in a gel of 1% agarose in 1X TBE (Tris-HCl, borate, EDTA). In order to verify the specificity of the amplification products, 3 µl of each PCR product were analyzed in

agarose gel and then transferred onto a nylon membrane (Hybond® $-N^+$, Amersham) (Southern blot) using 0.4 N NaOH. The hybridization with the gag cl2 probe (1056 bp) (J. Sambrook et al., 1989) was carried out under the following conditions: after prehybridization for 4 hours (in 5X SSC, 1X Denhardt's, 0.1% SDS, 50% formamide, 20 mM Tris-HCl, pH = 7.5, and 0.1 mg/ml of herring sperm DNA), the nylon membrane was hybridized (in 5X SSC, 1X Denhardt's, 0.1% SDS, 50% formamide, 20 mM Tris-HCl, pH = 7.5, 0.1 mg/ml of herring sperm DNA and 5% dextran sulfate), for 18 hours at 42°C with the ^{32}P-labeled gag DNA probe. The gag PCR products from each isolated human chromosome were washed once, for 15 min at room temperature, in a solution of 2X SSC, 0.2% SDS; twice, for 15 min each wash at 65°C, in a solution of 0.2X SSC, 0.1% SDS; twice, for 15 min each at 65°C, in a solution of 0.1X SSC, 0.1% SDS; and twice, for 30 min each at room temperature, in a solution of 0.1X SSC, 0.1% SDS.

Part of the remaining volume (4 µl) of the PCR amplification products was used for the PTT "in vitro" transcription/translation test (Roest PAM et al., 1993) (Promega, France). The remaining volume was used for the cloning in the pCR® 2.1-TOPO vector (Invitrogen) in accordance with the instructions with the kit, and for the sequencing with the method recommended for using the "PRISM™ Ready Reaction Amplitaq® FS, DyeDeoxy™ Terminator" sequencing kit (Applied Biosystems, ref. 402119), and the automatic sequencing was carried out on Applied Biosystems 373A and 377 machines, according to the manufacturer's instructions.

The portion encoded (SEQ ID NO. 31) by the 2009 bp fragment (SEQ ID NO. 2) was amplified by PCR with the *Pwo* enzyme (5 U/µl) (Boehringer Manneim, France) using 1 µl of the minipreparation of the gag clone DNA (SEQ ID NO. 3) under the following conditions: 95°C 1 min,

60°C 1 min and 72°C 2 min for 25 cycles, with a final reaction volume of 50 µl, using the primers:
- 5' primer (*Bam* HI) (SEQ ID NO. 8):
5' ATG GGA AAC GTT CCC CCC GAG 3' (21 mer), and
- 3' primer (*Hind* III), identified by SEQ ID NO. 9
5[sic] GGC CTA AGG CAG ACT TTT GAA 3' (21 mer).

The fragment obtained after PCR was linearized with *Bam* HI and *Hind* III and subcloned into the pET28C and pET21C expression vectors (NOVAGEN) linearized with *Bam* HI and *Hind* III. The DNA of the 1089 bp fragment in the two expression vectors were sequenced according to the method recommended for using the "PRISM™ Ready Reaction Amplitaq® FS, DyeDeoxy™ Terminator" sequencing kit (Applied Biosystems, ref. 402119) and the automatic sequencing was carried out on Applied Biosystems 373A and 377 machines, according to the manufacturer's instructions.

The expression of the nucleotide sequence of the 1089 bp fragment of the gag clone by the pET28C and pET21C expression vectors is identified by SEQ ID NO. 10 and SEQ ID NO. 11, respectively.

2.2- "In vitro" transcription/translation test (PTT, Promega)

This test was carried out in order to pinpoint the human chromosomes which have open reading frames for the *gag* gene of the HERV-W family.

A mixture containing 12.5 µl of TNT® rabbit reticulocyte lysate (Promega), 1 µl of TNT® reaction buffer (Promega), 0.5 µl of TNT® RNA polymerase (Promega), 0.5 µl of a 1 mM mixture of amino acids minus methionine, 2 µl of ^{35}S-methionine (1000 Ci/mmol) at 10 mCi/µl (Amersham), 0.5 µl of RNasin® ribonuclease inhibitor at 40 U/µl, 4 µl of PCR amplification

products (equivalent to 1 µg) from each human chromosome and 4 µl of water, in a reaction volume of 25 µl, [lacuna]. This mixture was incubated at 30°C for 90 min.

The gag proteins corresponding to the products of transcription/translation of the *gag* gene of the HERV-W family from each human chromosome, amplified by PCR, were revealed by 10% polyacrylamide gel electrophoresis in the presence of sodium dodecyl sulfate (SDS)-PAGE after exposure of the gel to the X-ray film at room temperature in the presence of an amplifying screen.

The results are given in Table 2 hereinafter.

In this table, the number indicated under each chromosome corresponds to the molecular mass (kDa) of the proteins visualized in polyacrylamide gel in the presence of SDS.

Table 2

Chromo No. Rodent parent	Chromo No. Rodent parent	1 m	2 h	3 h	4 h	5 h	6 h	7 h	8 h	9 h	10 h	11 h	12 h	13 h	14 h	15 h	16 m	17 m	18 h	19 h	20 m	21 m	22 h	X h	Y h	Water
PCR gag	gag	28 23 18		45 25 20 17			23 18 17	22									14									

Example 3: Expression of the gag clone in *Escherichia coli*, and reaction with human sera

The coding region SEQ ID NO. 2 was expressed in *Escherichia coli*, and then the products thus expressed were tested against serum from patients suffering from MS, and also against serum from healthy patients.

The constructs pET28c-gag clone (1089 bp) and pET21C-gag clone (1089 bp) synthesize, in the BL21 (DE3) bacterial strain, an N-terminal and C-terminal fusion protein for the pET28C vector, and a C-terminal fusion protein for the pET21C vector, with 6 histidine residues and an apparent molecular mass of approximately 45 kDa, which are revealed by SDS-PAGE polyacrylamide gel electrophoresis (U.K. Laemmli, Cleavage of structural proteins during the assembly of the head of bacteriophage T4, Nature, 1970, 227: 680–685).

The reactivity of the protein with respect to an anti-histidine monoclonal antibody (DIANOVA) was demonstrated using the Western blot technique (H. Towbin et al., Electrophoretic transfer of proteins from polyacrylamide gels to nitrocellulose sheets: procedure and some applications, Proc. Natl. Acad. Sci. USA, 1979, 76: 4350-4354).

The recombinant proteins pET28C-gag clone (1089 bp) and pET21C-gag clone (1089 bp) were visualized, by SDS-PAGE, in the insoluble fraction after enzymatic digestion of the bacterial extracts with 50 µl of lysozyme (10 mg/ml) and lysis by ultrasound.

The antigenic properties of the recombinant antigens pET28C-gag clone (1089 bp) and pET21C-gag clone (1089 bp) were tested by Western blot after solubilization of the bacterial pellet with 2% SDS and

50 mM β-mercaptoethanol. After incubation with the sera from patients suffering from multiple sclerosis, the sera from the neurological controls and the blood transfusion center (BTC) control sera, the immunocomplexes were detected using an alkaline phosphatase-coupled anti-human IgG and IgM goat serum.

The results are given in Table 3 hereinafter.

Table 3

Reactivity of sera from patients suffering from multiple sclerosis and controls, with the recombinant gag protein produced in *E. coli*[a]

DISEASE	NUMBER OF INDIVIDUALS TESTED	NUMBER OF POSITIVE INDIVIDUALS
MS	15	6 2(+++), 2(++), 2(+)
NEUROLOGICAL CONTROLS	2	1(+++)
HEALTHY CONTROLS (BTC)	22	1(+/-)

(a) The strips containing 1.5 µg of recombinant gag antigen show reactivity against sera diluted 100-fold. The Western blot interpretation is based on the presence or absence of a gag-specific band on the strips. Positive and negative controls are included in each experiment.

These results show that, under the technical conditions used, approximately 40% of the human multiple sclerosis sera tested react with the recombinant gag protein.

CLAIMS

1. Nucleic acid fragment, characterized in that it consists of at least one portion of the *gag* gene of an endogenous retrovirus associated with an autoimmune disease, or with unsuccessful pregnancy or pathological conditions of pregnancy, said portion being chosen from SEQ ID NO. 2 and any series of contiguous nucleotides belonging to SEQ ID NO. 2 but not belonging to SEQ ID NO. 1 and encoding an expression product, or the sequence complementary to said fragment.

2. Fragment according to claim 1, characterized in that it can be isolated from at least one of human chromosomes 1, 3, 6, 7 and 16.

3. Fragment according to claim 2, characterized in that it can be isolated from at least chromosome 3.

4. Fragment according to claim 1, characterized in that the expression product is messenger RNA.

5. Fragment according to claim 1, characterized in that the expression product is immunologically recognized by antibodies present in a biological sample from a patient suffering from an autoimmune disease.

6. Fragment according to claim 5, characterized in that the autoimmune disease is multiple sclerosis.

7. Transcription product which can be obtained by transcription of at least said portion of the *gag* gene of a fragment according to any one of claims 1 to 6.

8. Method for detecting, in a biological sample, nucleotide sequences which are integrated into the DNA of the human genome and which belong to the gag gene of an endogenous retrovirus associated with an autoimmune disease, or with unsuccessful pregnancy or pathological conditions of pregnancy, characterized in that:

- a prior step of extraction of the cellular DNA of said biological sample is carried out, and then at least one cycle of amplification of the cellular DNA is carried out, for instance by PCR, using primers in particular chosen from SEQ ID NO. 4 to SEQ ID NO. 9 and SEQ ID NO. 12 to SEQ ID NO. 17,

- the cellular DNA present in the sample is brought into contact with a given probe which is capable of hybridizing with a said nucleotide sequence and of forming a hybridization complex, said probe comprising at least 15 contiguous nucleotides, preferably 17 and advantageously 19 contiguous nucleotides, of SEQ ID NO. 3, or consisting of SEQ ID NO. 3, under suitable conditions for the hybridization, in particular under conditions of high stringency, and

- the hybridization complexes formed are detected by any suitable means.

9. Method according to claim 8, characterized in that the probe is labeled with a tracer, such as for example a radioactive tracer or an enzyme.

10. Method for detecting, in a biological sample, nucleotide sequences which are integrated into the

DNA of the human genome and which belong to the gag gene of an endogenous retrovirus associated with an autoimmune disease, or with unsuccessful pregnancy or pathological conditions of pregnancy, characterized in that:

- a prior step of extraction of the cellular DNA of said biological sample, optionally derived from isolated chromosomes, is carried out, and then at least one cycle of amplification of the cellular DNA is carried out, for instance by PCR, using primers in particular chosen from SEQ ID NO. 4 to SEQ ID NO. 9 and SEQ ID NO. 12 to SEQ ID NO. 17,

- a step of in vitro transcription/translation of the amplified product is carried out, and

- the product derived from the transcription/translation step is reacted with a serum or plasma from a patient with an autoimmune disease.

11. Method according to any one of claims 8 to 10, characterized in that the biological sample is a biological fluid chosen from serum, plasma, synovial fluid and urine.

12. Method for studying and/or monitoring T-cell proliferation in vitro, according to which the T cells from a patient are brought into contact with either transcription/translation products, as obtained according to the method of claim 11, or synthetic peptides belonging to SEQ ID NO. 31.

13. Method for the in situ molecular labeling of chromosomes isolated from patients, in which a

probe labeled with any suitable tracer, and comprising all or part of SEQ ID NO. 3, is used.

14. Recombinant protein obtained using an expression cassette in a bacterial host, characterized in that its protein sequence consists of SEQ ID NO. 31.

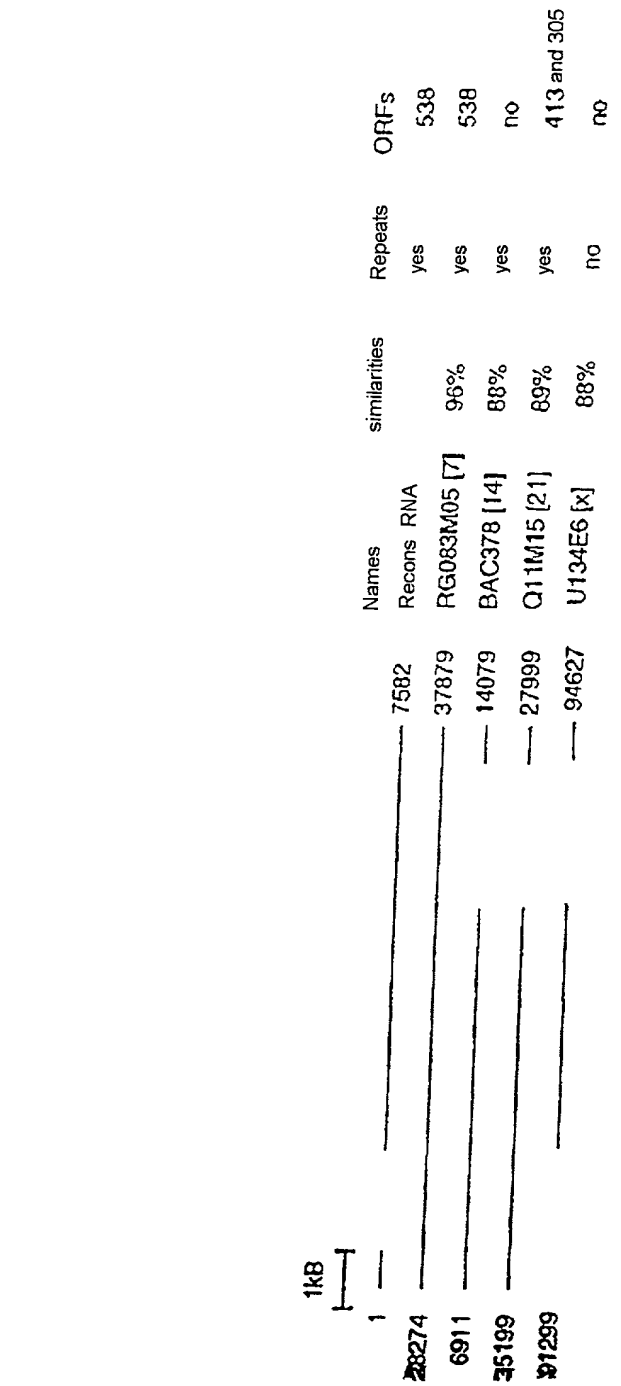
15. Protein according to claim 14, characterized in that the bacterial host is *E. coli*.

16. Reagent for detecting, in a biological sample, an autoimmune disease or monitoring pregnancy, comprising at least one fragment according to any one of claims 1 to 6, one transcription/translation product, as obtained according to the method of claim 11, one synthetic peptide belonging to SEQ ID NO. 31 or one protein according to claim 15 or 16.

17. Use of a fragment according to any one of claims 1 to 6, of a transcription/translation product, as obtained according to the method of claim 11, of a synthetic peptide belonging to SEQ ID NO. 31 or of a protein according to claim 15 or 16, for detecting, in a biological sample, susceptibility to an autoimmune disease, or monitoring pregnancy.

18. Use according to claim 17, characterized in that the autoimmune disease is multiple sclerosis.

FIG 1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no
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FIG 1

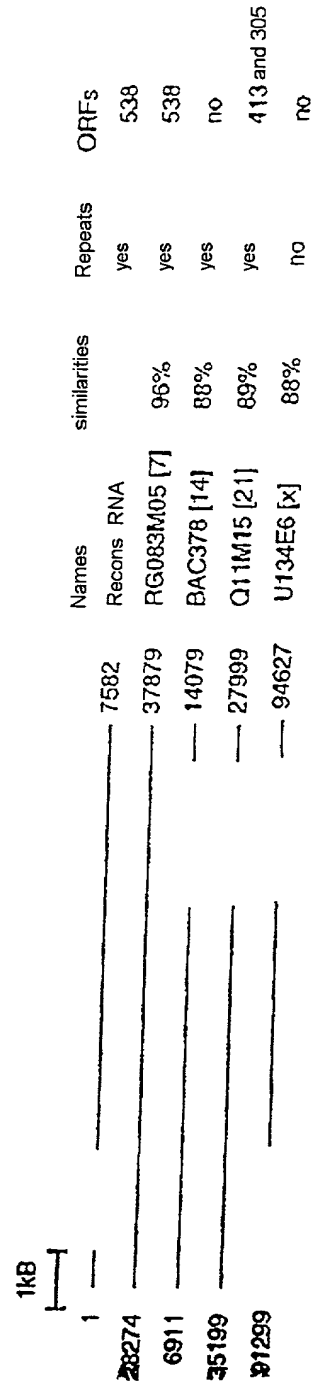
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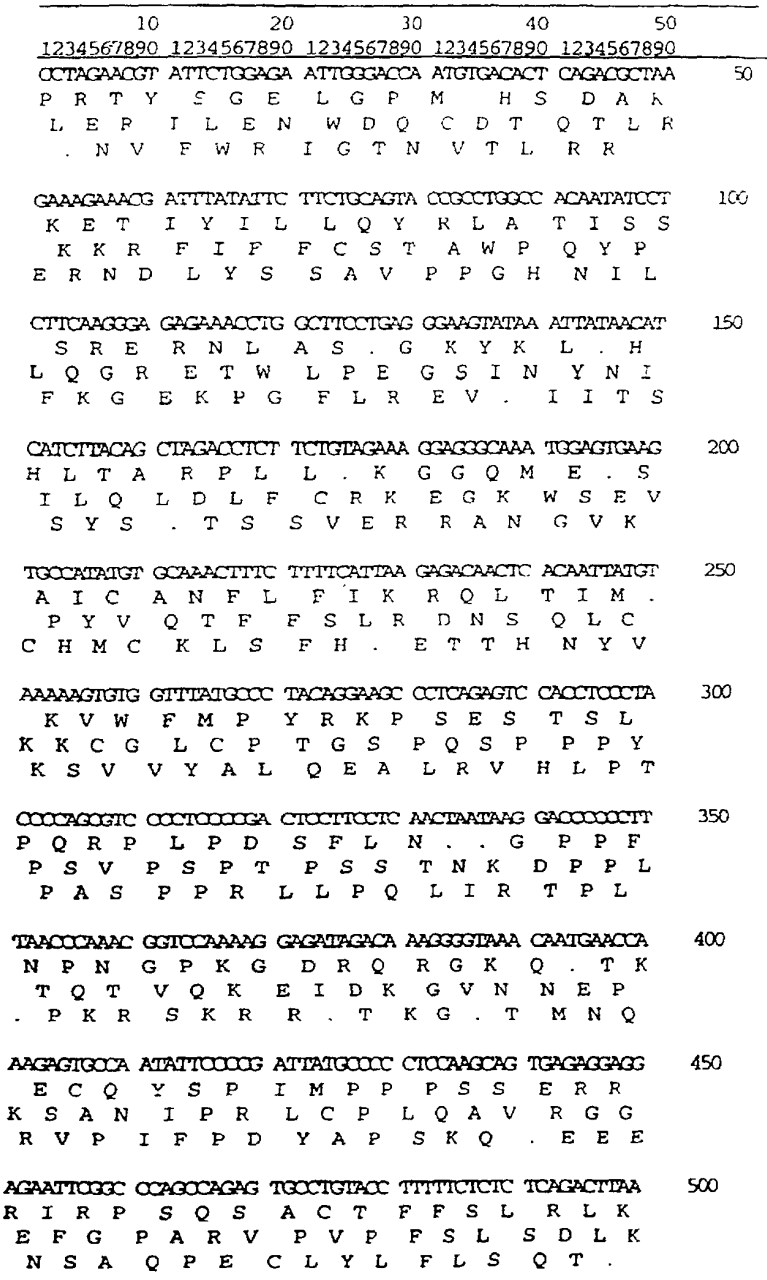
FIG 2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L E P I L E N W D Q C D T Q T L R
. N V F W R I G T N V T L R R
GAAAGAAACG ATTTATATTC TTCTGCAGTA CCGCCTGGCC ACAATATCCT 100
K E T I Y I L L Q Y R L A T I S S
K K R F I F F C S T A W P Q Y P
E R N D L Y S S A V P P G H N I L
CTTCAAGGGA GAGAAACCTG GCTTCCTGAG GGAAGTATAA ATTATAACAT 150
S R E R N L A S . G K Y K L . H
L Q G R E T W L P E G S I N Y N I
F K G E K P G F L R E V . I I T S
CATCTTACAG CTAGACCTCT TCTGTAGAAA GGAGGGCAAA TGGAGTGAAG 200
H L T A R P L L . K G G Q M E . S
I L Q L D L F C R K E G K W S E V
S Y S . T S S V E R R A N G V K
TGCCATAIGT GCAAACTTTC TTTTCATTAA GAGACAACTC ACAATTATGT 250
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P Y V Q T F F S L R D N S Q L C
C H M C K L S F H . E T T H N Y V
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K S V V Y A L Q E A L R V H L P T
CCCCAGCGTC CCCTCCCCGA CTCCTTCCTC AACTAATAAG GACCCCCCTT 350
P Q R P L P D S F L N . . G P P F
P S V P S P T P S S T N K D P P L
P A S P P R L L P Q L I R T P L
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N P N G P K G D R Q R G K Q . T K
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AAGAGTGCCA ATATTCCCCG ATTATGCCCC CTCCAAGCAG TGAGAGGAGG 450
E C Q Y S P I M P P P S S E R R
K S A N I P R L C P L Q A V R G G
R V P I F P D Y A P S K Q . E E E
AGAATTCGGC CCAGCCAGAG TGCCTGTACC TTTTCTCTCC TCAGACTTAA 500
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N S A Q P E C L Y L F L S Q T .

FIG 2 (continued)

```
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  Q I K  I D L  G K P S  D N P  D G Y
S K L K    T    V N S  Q I T L  T A I

ATTGATGTTT TACAAGGGTT AGGACAATCC TTTGATCTGA CATGGAGAGA   600
  . C F  T R V  R T I L  . S D  M E R
I D V L  Q G L  G Q S  F D L T  W R D
 L M F  Y K G  . D N P  L I .  H G E I

TATAATGTTA CTACTAAATC AGACACTAAC CCCAAATGAG AGAAGTGCCG   650
Y N V T  T K S  D T N  P K .  E K C R
 I M L  L L N  Q T L T  P N E  R S A A
  . C Y  Y . I  R H .  P Q M R  E V P

CTGTAACTGC AGCCCGAGAG TTTGGCGATC TTTGGTATCT CAGTCAGGCC   700
 C N C  S P R V  W R S  L V S  Q S G Q
  V T A  A R E  F G D L  W Y L  S Q A
L . L Q  P E S  L A I  F G I S  V R P

AACAATAGGA TGACAACAGA GGAAAGAACA ACTCCCACAG GCCAGCAGGC   750
  Q . D  D N R  G K N N  S H R  P A G
N N R M  T T E  E R T  T P T G  Q Q A
 T I G  . Q Q R  K E Q  L P Q  A S R Q

AGTTCCCAGT GTAGACCCTC ATTGGGACAC AGAATCAGAA CATGGAGATT   800
S S Q C  R P S  L G H  R I R T  W R L
 V P S  V D P H  W D T  E S E  H G D W
  F P V  . T L  I G T Q  N Q N  M E I

GGTGCCACAA ACATTTGCTA ACTTGCGTGC TAGAAGGACT GAGGAAAACT   850
 V P Q  T F A N  L R A  R R T  E E N .
  C H K  H L L  T C V L  E G L  R K T
G A T N  I C .  L A C  . K D .  G K L

AGGAAGAAGC CTATGAATTA CTCAATGATG TCCACTATAA CACAGGGAAA   900
  E E A  Y E L  L N D V  H Y N  T G K
R K K P  M N Y  S M M  S T I T  Q G K
 G R S  L . I  T Q .  C P L .  H R E R

GGAAGAAAAT CTTACTGCTT TTCTGGACAG ACTAAGGGAG GCATTGAGGA   950
G R K S  Y C F  S G Q  T K G G  I E E
 E E N  L T A F  L D R  L R E  A L R K
  K K I  L L L  F W T D  . G R  H . G

AGCATACCTC CCTGTCACCT GACTCTATTG AAGGCCAACT AATCTTAAAG  1000
 A Y L  P V T .  L Y .  R P T  N L K G
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FIG 2 (continued)

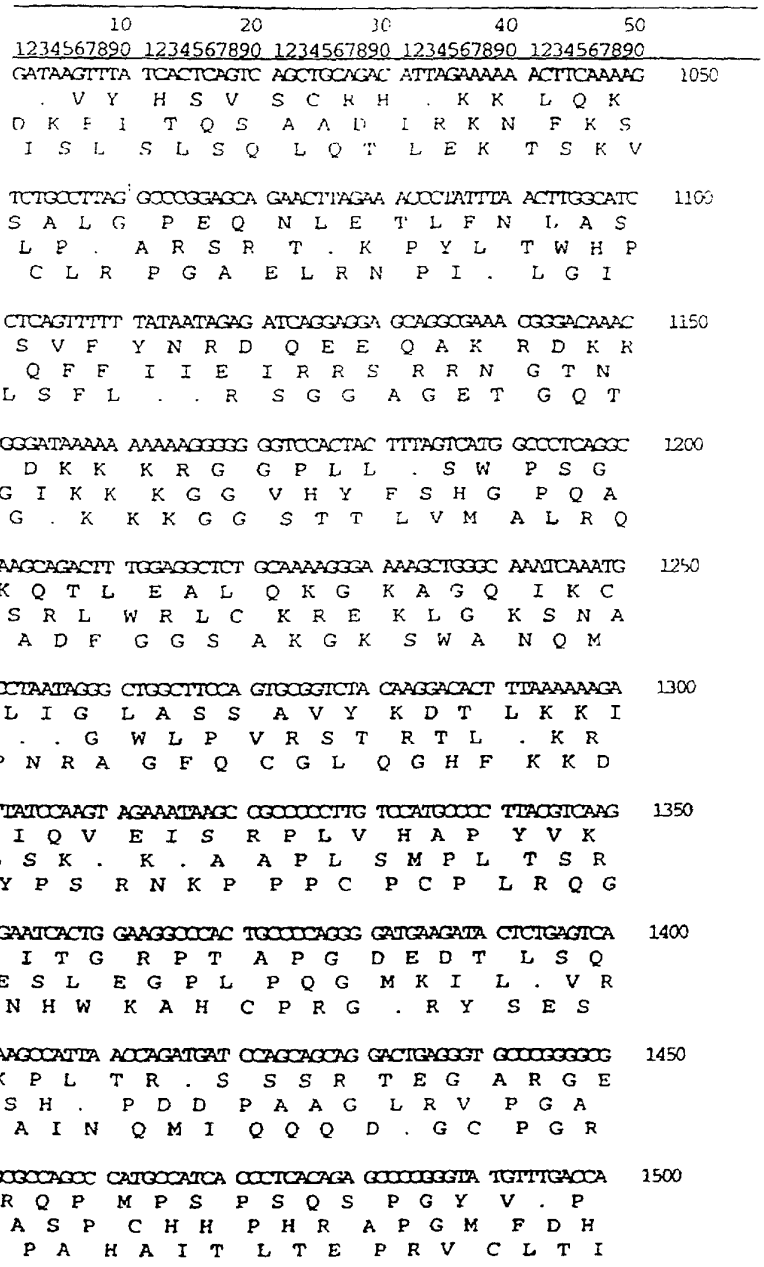

FIG 2 (continued)

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TTGAGAGCCA A                                          1511
L  R  A
 .  E  P
 F  S  Q
```

Docket No.:

DECLARATION AND POWER OF ATTORNEY UNDER 35 USC §371(c)(4) FOR PCT APPLICATION FOR UNITED STATES PATENT

As a below named inventor, I hereby declare that:
my residence, post office address and citizenship are as stated below under my name;

I verily believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought, namely the invention entitled: Endogeneous nucleic acid fragment associated with an autoimmune disease, labeling method and reagent

described and claimed in international application number PCT FR00/00144 filed 21th January 2000 .

I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations §1.56.

Under Title 35, U.S. Code §119, the priority benefits of the following foreign application(s) filed by me or my legal representatives or assigns within one year prior to my international application are hereby claimed:

France N° 99/00888 filed on 21th January 1999

The following application(s) for patent or inventor's certificate on this invention were filed in countries foreign to the United States of America either (a) more than one year prior to my international application, or (b) before the filing date of the above-named foreign priority application(s):

I hereby appoint the following as my attorneys of record with full power of substitution and revocation to prosecute this application and to transact all business in the Patent Office:

James A. Oliff, Reg. No. 27,075; William P. Berridge, Reg. No. 30,024; Kirk M. Hudson, Reg. No. 27,562; Thomas J. Pardini, Reg. No. 30,411; Edward P. Walker, Reg. No. 31,450; Robert A. Miller, Reg. No. 32,771; Mario A. Costantino, Reg. No. 33,565; Caroline D. Dennison, Reg. No. 34,494; and Stephen J. Roe, Reg. No. 34,463.

ALL CORRESPONDENCE IN CONNECTION WITH THIS APPLICATION SHOULD BE SENT TO OLIFF & BERRIDGE, PLC, P.O. BOX 19928, ALEXANDRIA, VIRGINIA 22320, TELEPHONE (703) 836-6400.

I hereby declare that I have reviewed and understand the contents of this Declaration, and that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

1 ***Typewritten Full Name of Sole or First Inventor*** /-00

Given Name	Middle Initial	Family Name
Glaucia		PARANHOS-BACCALA

2 **Inventor's Signature** GLAUCIA PARANHOS-BACCALA

3 **Date of Signature**

Month	Day	Year
07	18	2001

Residence: 69003 LYON (City) — (State or Province) — France (Country)

Citizenship: SWISS

Post Office Address: 75 Cours Gambetta 69003 LYON (France)
(Insert complete mailing address, including country)

Note to Inventor: Please sign name on line 2 exactly as it appears in line 1 and insert the actual date of signing on line 3.

IF THERE IS MORE THAN ONE INVENTOR USE PAGE 2 AND PLACE AN "X" HERE X

(Discard this page in a sole inventor application)

2-00

1 ***Typewritten Full Name of Joint Inventor*** François MALLET
Given Name | Middle Initial | Family Name

2 **Inventor's Signature:** François Mallet

3 **Date of Signature:** 7 | 17 | 2001
Month | Day | Year

Residence: 69100 VILLEURBANNE FRX France
City | State or Province | Country

Citizenship: French

Post Office Address: 84 Rue Anatole France 69100 VILLEURBANNE (France)
(Insert complete mailing address, including country)

3-00

1 ***Typewritten Full Name of Joint Inventor*** Cécile VOISSET
Given Name | Middle Initial | Family Name

2 **Inventor's Signature:** Cécile Voisset

3 **Date of Signature:** 08 | 01 | 2001
Month | Day | Year

Residence: LONDON WC1H 9QW GBX GB
City | State or Province | Country

Citizenship: French

Post Office Address: 80 Clare Court Judd Street – LONDON WC1H 9QW (GB)
(Insert complete mailing address, including country)

1 ***Typewritten Full Name of Joint Inventor***
Given Name | Middle Initial | Family Name

2 **Inventor's Signature:**

3 **Date of Signature:**
Month | Day | Year

Residence:
City | State or Province | Country

Citizenship:

Post Office Address:
(Insert complete mailing address, including country)

1 ***Typewritten Full Name of Joint Inventor***
Given Name | Middle Initial | Family Name

2 **Inventor's Signature:**

3 **Date of Signature:**
Month | Day | Year

Residence:
City | State or Province | Country

Citizenship:

Post Office Address:
(Insert complete mailing address, including country)

Note to Inventor: Please sign name on line 2 exactly as it appears in line 1 and insert the actual date of signing on line 3.

This form may be executed only when attached to the first page of the Declaration and Power of Attorney of the application to which it pertains.

SEQUENCE LISTING

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